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EXAMINER	
WEBSTER, DAVID D	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,871	ROSCHER ET AL.	
	Examiner	Art Unit	
	DAVID D. WEBSTER	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 19* is/are pending in the application.

4a) Of the above claim(s) *14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/22/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The application claims national stage entry for PCT/EP05/50799 filed 02/25/2005 for the instant application 10589871, filed 9/12/2006. The date is within the pendency and allotted time frame. The priority date is set 02/25/2005.

Claims 1-13 and 19 are under consideration.

1. Applicant's election without traverse of claims 1-13 and 19 in the reply filed on 01/21/2009 is acknowledged.

2. Claims 14-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group II, there being no allowable generic or linking claim. Election was made without traverse in the reply filed 01/21/2009.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor or at least one claim remaining in the application. Any amendment of the inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48 (b) and by the fee required under 37 CFR 1.17 (h).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of combination either free or fixed combination for the use of Ciclesonide with glycopyrronium and the enantiomers, does not reasonably provide enablement for solvate or physiologically functional derivative. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of

experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Because the specification, while being enabling for the claimed compounds per se, isomers of the claimed compounds per se, or salts of the claimed compounds per se, does not reasonably provide enablement for solvates of the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

SOLVATES

Solvates are crystal forms of a compound that encompass solvent molecules in the structure. Although solvates of known pharmacologically active agents are known, one skilled the art can not predict which compounds will form solvates

and which will not. Methodology for forming solvates differs from compound to compound and although general methods that are routinely attempted exist, it is unpredictable whether they will result in formation of a solvate of any specific compound.

Since solvates are essentially crystalline forms of compounds, and it is acknowledged that crystal forms of compounds are unpredictable in their formation, formation of solvates is also necessarily unpredictable. There is no way for one skilled in the art to know, a priori, if a hydrate or solvate of a given compound even exists. For example, Vippagunta (Adv. Drug Del. Rev., 2001, vol. 48, 2001, pp. 3-26) teaches that the main challenges in managing the phenomenon of multiple solid forms of a drug is the inability to predict the number of forms that can be expected in a given case (page 11, fight column). Furthermore, Vippagunta flatly states on page 18, section 3.4 the following: "Predicting the formation of solvates or hydrates of a compound...is complex and difficult." Thus, the state of the prior art does not support the broad scope of the above claims.

FUNCTIONAL DERIVATIVES

Functional Derivatives or as the specification has stated physiologically functional derivatives are related to both of dual pharmaceutical compounds which act and function like the two active ingredients within the pharmaceutical formulation. The two compounds of interest are for the use of respiratory disease namely asthma. The compounds which are described

within the claims are glycopyrronium specifically 3-[(Cyclopentyl-hydroxyphenylacetyl) oxy]-l, l-dimethylpyrrolidinium bromide and Ciclesonide specifically [11 beta, 16 alpha (R)]-16, 17-[(Cyclohexylmethylen) bis (oxy)]-11-hydroxy-21-(2-methyl-1-oxoproproxy) pregna-1, 4-dien-3, 20-dion as well as acceptable salts, their solvates, physiologically functions derivates. However, the definition of physiological functional derivates have not been addressed and either within the specifications. While there has been further disclosure within the specification and limitation within the claims of the enantiomer and stereoisomers of glycopyrronium, there is not any discussion of physiological function derivatives. Functional derivates of compounds and their respective interactions with active site have been studied with respect to their active interactions with the hydrophilic and hydrophobic interactions as well as hydrogen binding options. There are selective amino acids which bind and act within these sites. Some of them are histidine, serine, arginine, and glutamic acid which have been the noted to have the proper side chains which have strong affinity for binding of and through the hydrogen bonding. Each selective nucleophilic and electrophilic groups of the compound has the ability to interact with the hydrogen or free binding pair of electrons respectively. The distances, side chain proximity and other interactions necessary for the proper affinity/avidity are well known for the interactions to occur. The functional derivates are predisposed to the limitations indicated above with the active and receptors sites which the active pharmaceutical agents are designed. Whether

the site is an enzyme active or receptor site the interactions with the compounds and sites have been indicate within common texts of Biochemistry. It is one of the oldest concepts in enzymology and stated in Basic Concepts in Biochemistry, by Gilbert, H. F., 2nd Edition pg 83 and 83. The lock and key concept has been discussed and noted and is common knowledge with those skilled in the art.

The number of biological functional derivatives covers a number different structure which can function in the active sites for the dual pharmaceutical agents. The specifics which were are not covered in the specification or claims. Additionally, they also encompass the carrier sugars and their interaction with the pharmaceutical agent and with the dry powder carrier. The chemical derivatives, carrier sugar/derivatives and dry powder carrier/derivatives were not discussed in the specification or narrowed in the claims. The broad scope of solvates, chemical derivative, carrier sugar/derivatives, dry powder carrier/derivatives as described in claims without further limitation as well as the lack of working examples and discussion in specification would make it unpredictable for one of skill in the art to practice the full scope of the claimed invention without an undue amount of experimentation.

Claims 2 and 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for free and fixed combination; the

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use. While the specification does provide information about what is meant by free and fixed combination. It does not provide any specific examples and demonstrate the claims how to use free and fixed combinations. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the invention commensurate in the scope with the claims. The claims do not further limit or describe the how free and fixed combinations are to be used with the invention. The information cited above is Scope of Enablement Rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands', 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing Exparte Forman, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,

6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108,427 F.2d 833,839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands"

factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment or prophylaxis of respiratory disease with combinations of ciclesonide with glycopyrronium. While on page 4 of the specification it defines fixed combination as the compounds of the instant claimed inventions to be administered simultaneously in the same pharmaceutical formulation or in different formulations (free combinations) or sequentially ordered. There is no further limitation of the definition of fixed and free to enable one to reproduce the invention. It further does not state which order is best method for the free combination.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), Nationwide Chemical Corporation, et al. v. Wright, et al., 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), Ex parte Sudilovsky 21 USPQ2d 1702 (Appellant's invention)

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1 As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not experimentation.

2. Breadth of the claims

While it is the nature to further focus the elements from claim to claim and to further narrow the invention and define the invention the inventors have not addressed this with respect to solvates, biological function derivative, free and fixed combination. Thusly, solvate, function derivative, free and fixed combination usage and terminology also generic. So as a result, they have broad and nonspecific classifications.

3. The amount of direction or guidance provided and the presence or absence of working examples.

The claims provide no direction or guidance for determining the particular administration regimens (e.g., dosages, timing, administration routes, etc.) necessary to treat all of the various respiratory diseases, particularly in humans. The claims do address inhalation with a sugar carrier, solvate, and functional derivative. They do not talk about ratio of the carrier, and active agents. They do not provide ratio of the active agents. While the specification on page 6 talks about the associated problems with associated with stability of the formulations the claims do not. It can only be presumed from the narrowing of the enantiomer selected and the enrichment of the enantiomer that stability one of the issues. The claims and specification together does not further one to be able to use claims 2 and 3. It does not provide reasonable means to make the invention.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed supra) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used as a treatment and/or prevention of various types of respiratory conditions/symptoms as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant application 10589871 there are the following variables ciclesonide, glycopyrronium, free and fixed combinations, enantiomeric purity. The claims do not further limit concentration, ratio, method of administration with the claims free and fixed combination to allow one to further enhance or reproduce the invention.

5) the predictability of the art

While there has been further disclosure within the specification and limitation within the claims of the enantiomer and stereoisomers of glycopyrronium, there is not any discussion of physiological function derivates. Functional derivates of compounds and their respective interactions with active site have been studied with respect to their active interactions with the hydrophilic and hydrophobic interactions as well as hydrogen binding options. There are selective amino acids which bind and act within these sites. Some of them are histidine, serine, arginine, and glutamic acid which have been the noted to have the proper side chains which have strong affinity for binding of and through the hydrogen bonding. Each selective nucleophilic and electrophilic groups of the compound has the ability to interact with the

hydrogen or free binding pair of electrons respectively. The distances, side chain proximity and other interactions necessary for the proper affinity/avidity are well known for the interactions to occur. The functional derivates are predisposed to the limitations indicated above with the active and receptors sites which the active pharmaceutical agents are designed. Whether the site be a enzyme active or receptor site the interactions with the compounds and sites have been indicate within common texts of Biochemistry notably Lehninger, A and Stryer, L. The lock and key concept has been discussed and noted and is common knowledge with those skilled in the art.

The number of biological functional derivatives covers a number different structure which can function in the active sites for the dual pharmaceutical agents. The specifics which were are not covered in the specification or claims. Additionally, they also encompass the carrier sugars and their interaction with the pharmaceutical agent and with the dry powder carrier. The chemical derivatives, carrier sugar/derivatives and dry powder carrier/derivatives were not discussed in the specification or narrowed in the claims.

While it is true that each and every stereoisomer and enantiomer has some given commonalities the exact structure of the adjacent atoms (molecules) and resonance structures of each provide difference in the method of handling and problems with associated stability. In other words each and every compound which has chiral compound has different characteristics. These are notable

different with respect to sensitivity to moisture and interactions with other compounds whether they be carrier or the other active groups in the compound or other active agents. While the specification and claims address in very broad terms some of these problems it nevertheless does not allow one to reproduce or vaguely have high degree of certainty to make or improve the invention.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 10-13, 19 are rejected under 35 U.S.C. § 102(b) anticipated by US Patent 6,645,466 B1. as evidenced by STN registry for glycopyrronium and Ciclesonide

Claim 1 recites a pharmaceutical formulation comprising a pharmaceutical acceptable salt of glycopyrronium, a solvate or physiologically functional derivative thereof in combination with Ciclesonide, a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a pharmaceutically acceptable carrier and/or one or more excipients.

US patent 6645466 teaches the following: in column 6 lines 53-64, the use of magnesium stearate in dry powder formulations which contain a beta-mimetic and/or an anticholinergic and/or a corticosteroid is particularly preferred, and in particular in dry powder formulations which contain a beta-mimetic and/or an anticholinergic and/or a corticosteroid in the form of a pharmaceutically acceptable salt or ester, for example a beta-mimetic in the form of a salt, such as levalbuterol sulfate, formoterol fumarate, formoterol tartrate, salbutamol sulfate or salmeterol xinafoate (salmeterol 1-hydroxy-2-naphthoate), or an anti-cholinergic in the form of a salt, such as

oxitropium bromide, glycopyrrolate (glycopyrronium bromide). According to a further preferred aspect, the formulations obtainable according to the invention can in particular also contain a corticosteroid, such as Ciclesonide

Claim 2 recites the formulation according to claim 1, wherein the pharmaceutical acceptable salt of glycopyrronium and Ciclesonide are contained in the same pharmaceutical formulation (fixed combination).

Claim 1 is rejection is above.

US patent 6645466 teach the following: in column 6 lines 53-64, he use of magnesium stearate in dry powder formulations which contain a beta-mimetic and/or an anticholinergic and/or a corticosteroid is particularly preferred, and in particular in dry powder formulations which contain a beta-mimetic and/or an anticholinergic and/or a corticosteroid in the form of a pharmaceutically acceptable salt or ester, for example a beta-mimetic in the form of a salt, such as levalbuterol sulfate, formoterol fumarate, formoterol tartrate, salbutamol sulfate or salmeterol xinafoate (salmeterol 1-hydroxy-2-naphthoate), or an anti-cholinergic in the form of a salt, such as oxitropium bromide, glycopyrrolate (glycopyrronium bromide) ..... According to a further preferred aspect, the formulations obtainable according to the invention can in particular also contain a corticosteroid, such as Ciclesonide.

Claim 3 recites the formulation according to claim 1, wherein the pharmaceutical acceptable salt of glycopyrronium and Ciclesonide are contained in different pharmaceutical formulations (free combination).

Claim 1 is rejection is above.

US patent 6645466 teach the following: in column 6 lines 53-64, the use of magnesium stearate in dry powder formulations which contain a beta-mimetic and/or an anticholinergic and/or a corticosteroid is particularly preferred, and in particular in dry powder formulations which contain a beta-mimetic and/or an anticholinergic and/or a corticosteroid in the form of a pharmaceutically acceptable salt or ester, for example a beta-mimetic in the form of a salt, such as levalbuterol sulfate, formoterol fumarate, formoterol tartrate, salbutamol sulfate or salmeterol xinafoate (salmeterol 1-hydroxy-2-naphthoate), or an anti-cholinergic in the form of a salt, such as oxitropium bromide, glycopyrrolate (glycopyrronium bromide) ..... According to a further preferred aspect, the formulations obtainable according to the invention can in particular also contain a corticosteroid, such as Ciclesonide. Further example of different types of formulations (free combination) are: The dry powder formulations obtainable according to the invention thus comprise a pharmaceutically inactive carrier of noninhalable particle size, a finely divided pharmaceutically active compound of inhalable particle size (i.e. having a mean particle diameter of preferably at most 10 um, in particular at most 5 um) and--to improve the resistance to moisture--magnesium stearate, and they are

preferably present in the form of "interactive (or ordered or adhesive) mixtures". If desired, the dry powder formulations can also contain a proportion of carrier material of inhalable particle size. (column 4 and lines 57- 67)

The expression "interactive mixture" or "ordered mixture" or "adhesive mixture" is familiar to the person skilled in the art and in the context of the present invention comprises dry powder formulations in which the pharmacologically inactive carrier is present in a particle size which is noninhalable or mainly noninhalable, and in which microfine active compound particles are bound to the carrier particles by adhesion (i.e. are not contained in the carrier, e.g. in the form of granules). (column 5 and lines 1-10). While the words free and fixed combination are not directly taught there are associated. The above is the teaching in US 6645466 with respect to the mixture with the carriers. They are talking of the interactions with the carriers and the interactions of the carrier with active compounds. It is anticipated that the teachings of US 6645466 although not congruent and identical they can provide teachings to make up the necessary formulations for the intended potential use.

Claim 4 recites formulation according to claim 1, comprising a compound.....from the restriction they have selected have selected [11 beta, 16 alpha (R)]-16,17-[(Cyclohexylmethylen) bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxoproproxy) pregna-1,4-dien-3,20-dion (as selected in species election).

Claim 1 is rejection is above.

US patent 6645466 teach the following: in column 6 lines 53-64, he use of magnesium stearate in dry powder formulations which contain a beta-mimetic and/or an anticholinergic and/or a corticosteroid is particularly preferred, and in particular in dry powder formulations which contain a beta-mimetic and/or an anticholinergic and/or a corticosteroid in the form of a pharmaceutically acceptable salt or ester, for example a beta-mimetic in the form of a salt, such as levalbuterol sulfate, formoterol fumarate, formoterol tartrate, salbutamol sulfate or salmeterol xinafoate (salmeterol 1-hydroxy-2-naphthoate), or an anti-cholinergic in the form of a salt, such as oxitropium bromide, glycopyrrolate (glycopyrronium bromide) ..... According to a further preferred aspect, the formulations obtainable according to the invention can in particular also contain a corticosteroid, such as Ciclesonide. Additionally, as evidentiary evidence the CAS registry has named the above compound [11 beta, 16 alpha (R)]-16,17-[(Cyclohexylmethylen) bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxoproproxy) pregna-1,4-dien-3,20-dion as Ciclesonide.

Claim 10 recites the formulation according to claim 1, which is suitable for administration by inhalation.

Claim 1 is rejection is above.

US 6645466 teaches the elements of claim 1 of instant application as referenced above; furthermore in claim 1 of the same patent as indicated from use in dry powder formulation for inhalation and lastly in column 5 lines 58 to 65 there is information which address individual does in multidose inhalers

Claim 11 recites the formulation according to claim 1, which is suitable for nasal administration.

Claim 1 is rejection is above

US 6645466 teaches the elements of claim 1 of instant application as referenced above; furthermore in claim 1 of the same patent as indicated from use in dry powder formulation for inhalation. Further details of nasal administration found in column 1 and 2 within background of the invention. Also, in column 5 lines 58 to 65 there is information which addresses individual does in multidose inhalers.

Claim 12 recites the formulation according to claim 1 of instant application, which is a dry powder and the carrier is a saccharide.

Claim 1 is rejection is above

US 6645466 teach the elements of claim 1 as referenced above; furthermore in claim 4 of the '466 patent, specific reference to carriers of monosaccharide and in claim 1 address dry powder formulation.

Claim 13 recites the formulation according to claim 12, wherein the carrier is lactose monohydrate.

Claim 12 is rejection is above

US 6645466 teach the elements of claim 12 and 1 as referenced above; furthermore in claim 4 of the '466 patent, specific reference to carriers of lactose monohydrate and in claim 1 address dry powder formulation.

Claim 19 recites a dry powder inhalation product comprising a pharmaceutical composition according to claim 13.

Claim 13 is rejection is above

US 6645466 teaches the elements of claim 13 and 1 of instant application as referenced above; furthermore in claim 1 of the same patent as indicated from use in dry powder formulation for inhalation and further indicated taught in claims 7, 14 and 15... It is anticipated with the teachings of the US 6645466 with respect to the use of pharmaceutical active compounds then they are to be used in pharmaceutical composition or formulation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 5-8 are rejected under 35 U.S.C. § 103 as being unpatentable over US Patent 6,645,466 in view of US Patent 6,613,795.

Previously, Claim 1 was rejected under 35 U.S.C. § 102(b) as anticipated by US Patent 6,645,466 B1.

i) US Patent 6,645,466 B1 teaches in column 6, lines 13 – 36 the use of both glycopyrronium and Ciclesonide chiral active compounds can be present in the form of an optical isomer, a diastereoisomeric mixture of racemate. In the case of the chiral active compounds, they can be present in the form of an optical isomer, a diastereoisomeric mixture of racemate. If desired, the formulations according to the invention can contain two or more pharmaceutically active compounds. In column 6 lines 38 to 51 give examples of the various pharmaceutical salts as a result of compounds related to

problems with moisture as a result of changes due to exposure to moisture. Additionally, it states in the case of chiral active isomer, a diastereoisomeric mixture of racemate. If desired the formulations according to the invention can contain two or more pharmaceutically active compounds. Furthermore it states, "the moisture sensitivity is frequently a great problem especially in the case of active compounds which are present as a salt or ester " .....Also within column 6, line 52-58 there is the use of it; the desired formulations according to the invention can contain two or more pharmaceutically active compounds. In the two preceding paragraphs the mixture can be mixed with variety of salt, sugars in dry formulation which contain anywhere from 1-6 active compounds. Later on in column 7 lines 12-22 the range of the mixtures and their active prospective formulation can vary with wide ranges dependent on the respective active compound second paragraph. The dry formulation is active and more stable when application is in the dry form. Additionally, in same paragraph addresses the advantages of dry salts in preservation of the active compounds.

ii) The 6,645,466 Patent does not teach us of the specific ratio of enantiomerically enriched compounds racemic forms [S, S-, S, R, R, S-and R, R] of glycopyrronium for the preferred effectiveness. Although it does specifically state in column 6, lines 13-36 the use optical isomer, and the use a diastereoisomeric mixture of racemate. The '466 patent has noted it has optical centers and the possibility of the mixtures of these in use.

iii) US 6613795 teaches the use and method of treatment of obstructive respiratory diseases by inhalative administration of a pharmaceutically suitable salt of the enantiomerically pure ester (3R,2'R) at a 90% purity level of the glycopyrronium up to 98 % level in claims 1 through 5 and teaches (3S, 2'R) from at 90 % to 98 % purity level of glycopyrronium.

iv) The elements of claim 1 are fully addressed within the 35 USC 102 rejection stated above. For claim 5; one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the enantiomerically enriched compounds racemic forms [S, S-, S, R, R, S-and R, R] of glycopyrronium taught by US Patent 6,613,795 for the glycopyrronium taught by US Patent 6,645,466 because the use of enantiomeric excess for a method of treatment due to the problems associated with the necessary active groups and the degradation. The sometimes degradation of active group(s) and chiral rearrangement (ethers) with exposure to moisture and associated method problems as stated above in paragraph i) {column 6 references, lines 13 – 36, lines 38 to 51 } as well as from the teachings in column 7 in paragraphs 2 and 3.

For claims 6, 7 and 8; US patent 6613795 teaches the use of R, R and S, S forms of the glycopyrronium compound in claims 1-5 in enantiomeric excess from a range of 90 % to 98 % for both the R, R and S, S. It would be obvious to

use the R, R enantiomer, enriched and by itself as well as the pharmaceutically acceptable salt. As stated in the teachings there are losses due to moisture content with the sometime degradation of active group(s) and chiral rearrangement. Additionally, it is expected that to increasing the overall percentage of the enantiomer helps with i) dose reproducibility; ii) lose due to packing problems with the dry carriers; iii) degradation of the active groups and chiral rearrangement and iv) shelf life the associated efforts with dose reproducibility. From the teachings of the references, it is apparent that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the enatiomers taught by the '795 patent instead of those taught by the '466 patent because with i) dose reproducibility; ii) lose due to packing problems with the dry carriers; iii) degradation of the active groups and chiral rearrangement and iv) shelf life the associated efforts with dose reproducibility and that said skilled artisan would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Claims 1 and 9 are rejected under 35 U.S.C. § 103 as being unpatentable over US Patent 6,645,466 in view of US Patent 5133974.

i) US Patent 6,645,466 B1 teaches in column 6, lines 13 – 36 the use of both glycopyrronium and Ciclesonide chiral active compounds can be present in the form of an optical isomer, a diastereoisomeric mixture of racemate. In the case of the chiral active compounds, they can be present in the form of an optical isomer, a diastereoisomeric mixture of racemate. If desired, the formulations according to the invention can contain two or more pharmaceutically active compounds. In column 6 lines 38 to 51 give examples of the various pharmaceutical salts as a result of compounds related to problems with moisture as a result of changes due to exposure to moisture. Additionally, it states in the case of chiral active isomer, a diastereoisomeric mixture of racemate. If desired the formulations according to the invention can contain two or more pharmaceutically active compounds. Furthermore it states, "the moisture sensitivity is frequently a great problem especially in the case of active compounds which are present as a salt or ester " .....Also within column 6, line 52-58 there is the use of it; the desired formulations according to the invention can contain two or more pharmaceutically active compounds. In the two preceding paragraphs the mixture can be mixed with variety of salt, sugars in dry formulation which contain anywhere from 1-6 active compounds. Later on in column 7 lines 12-22 the range of the mixtures and their active prospective formulation can vary with wide ranges dependent on the respective active compound second paragraph. The dry formulation is active and more stable when application is in the dry form. Additionally, in

same paragraph addresses the advantages of dry salts in preservation of the active compounds.

ii) US Patent 6645466 does not teach us the use of the components use in mammals or humans. It does not teach us use in twice or once daily treatment. It does however talk about the use of inhalers and individual doses (column 5, line 58-64).

iii) US patent 5133974 on paragraph 50 of the study has limited the use of pseudoephedrine to a Once-A-Day use and in paragraph 48 dosed twice a day. In paragraphs 82-85 it talks about use with humans The '974 publication' does not teach the use of glycopyrronium and ciclesonide in a nasal spray.

iv) For claim 9 US patent 5133974 teaches that the use of pseudoephedrine and its release and pharmacokinetics profile can be used on a once a day or twice dosage for effectiveness. With the combined teachings of the US patent 6,645,466 B1 and 5133974 it would have been prima facie obvious to use the dual pharmaceutical composition of Ciclesonide and glycopyrronium either on an as needed basis (for asthma) or based upon long term effective once or twice a day frequency for respiratory disease. It is obvious to use it mammals and human because of stated used with inhaler. Furthermore, the amount and ratio would be congruent to the dual agents used, pharmacological kinetics or reaction and release from the carrier.

From the teachings of the references, it is apparent that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the dual agents with inhalers, in human treatment, in an amount and ratio to be effective for a twice or once a daily treatment of a clinical condition in a mammal (human). Furthermore, from the combined teachings salt of glycopyrronium with salt or derivative pharmaceutically acceptable carrier with or optionally without Ciclesonide as well as dose reproducibility. And use in human in treatment of clinical condition for which a corticosteroid and/or an anticholinergic agent is indicated. In summary a skilled artisan would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed pharmaceutical agents are functionally different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d (PTO Bd. Pat. App. & Int. 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID D. WEBSTER

whose telephone number is (571)270-7675. The examiner can normally be reached on M - Th, 8:30 - 4:30 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/DDW/

/Patrick J. Nolan/

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